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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 04/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/646,599	GODDARD ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-38 and 43-57* is/are pending in the application.

4a) Of the above claim(s) *9-27,29-34 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5-8, 28, 35-37, 43-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to the directives of the amendment filed 3/1/04, claim 5 has been amended Claims 5-38 and 43-57 remain pending. Claims 6, 8, 28, 35-37, 43-57 are now rejoined with the elected group. Claims 9-27, 29-34, 38 remain withdrawn from consideration.

Claims 5-8, 28, 35-37, 43-57 are examined in this Office action.

Applicants' arguments filed 3/1/04 have been considered and found not persuasive.

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-8, 28, 35-37, 43-57 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is lacking for the claimed invention. The specification does not show that any of the compounds falling within the scope of claim 5 can be used to promote apoptosis, to inhibit apoptosis, or to alter any cellular function. The specification describes various experiments, and results obtained therefrom, but the compound(s) used in these experiments fall within the scope of the formula given on page 13, line 3+. As stated on page 9, line

27, the term "LPA", without further qualification, is intended to refer to 18:1 LPA, i.e., the compound corresponding to the structure on page 13, line 3+ in which "R" is a C_{18} mono-unsaturated olefin. Most, if not all of the experiments were done on the "18:1 LPA", and no experiments were done on the reverse ester compounds of claim 5.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. Extrapolation from results obtained with "18:1 LPA" to the reverse ester compounds of claim 5 will lead to "unpredictable" results. For example, Genevieve (*Biochemical Journal* **368** (Pt 2) 447-59, 2002) discloses that the "R" enantiomer of N-palmitoyl-norleucinol-1-phosphate induced mitosis of IMR-90 fibroblasts, whereas the S-isomer induced apoptosis of these same cells. This compound (N-palmitoyl-norleucinol-1-phosphate) is closely related to at least one of the genera of compounds disclosed in the application, for example that recited on page 16, line 17+. The point is that this disclosure (Genevieve) supports the conclusion of "unpredictability" in structure/activity relationships involving apoptosis. In the disclosed study, changing one chiral center of the molecule not only eliminated the propensity to inhibit apoptosis, but actually resulted in the opposite effect on cells. The structural change in proceeding from 18:1 LPA to the compounds of claim 5 is much more

dramatic. The effects of such a structural change on propensity to induce apoptosis cannot be predicted.

In another study, Lee (*J Biol Chem* **264**, 14797, 1989) examined structure/activity relationships of compounds which activate protein kinase C. This enzyme is relevant in that it is an important element of the signal transduction cascade that regulates cell proliferation. This enzyme is also activated by phosphatidylserine, a compound which is structurally related to LPA. As was reported, minor structural alterations eliminated activity. For example, changing the structure from that of phosphatidylserine to phosphatidylserine methyl ester, or phosphatidylserinol eliminated activity. Thus, one can conclude that in endeavoring to influence cell proliferation using phospholipids, structure/ activity relationships are "unpredictable". Similarly, if the skilled artisan were to attempt to extrapolate from the *in vitro* activities of 18:1 LPA (instant specification) to the compounds of claim 5, "unpredictable" results would be obtained. In addition, there is no prior art of record which would lead the skilled artisan to believe that such an extrapolation can be made reliably. There is also no guidance in the specification as to how to use the claimed compounds to increase apoptosis, to decrease apoptosis, or to alter cellular function. The skilled lipid chemist would conclude therefore that "undue experimentation" would be required to use the compounds of claim 5 in accordance with the assertions of the specification.

✧

Claims 6, 8, 28, 35, 52 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 6 encompasses salts of reverse ester LPA's. However, claim 5, upon which claim 6 depends, does not encompass salts. Accordingly, the claim dependence is not proper.

- Claim 8 is drawn to a method of "treating apoptosis". However, as recognized by the specification on page 1, line 31+, apoptosis is "a normal physiological process". On this basis the claim is rendered indefinite, since the claim is proposing to "treat" an event that occurs in healthy humans. It is noted also that on page 12, line 27, it is stated that the term "treating apoptosis" means the following: "administering ... a treatment to effect beneficial or desired clinical results... including... diminishing apoptosis". However, even if this language were incorporated into claim 8, it would still be indefinite. What is "beneficial" *vis a vis* apoptosis? That is, given a disease, the skilled artisan can often guess what result might be considered beneficial. But given that apoptosis per se is being treated, and not a disease, it is unclear what one should consider to be beneficial. For example, if a person is stricken with cancer, would inhibition of apoptosis of the cancer cells be considered beneficial? If apoptosis is occurring in a given tissue of a completely healthy human, and administration of a compound of claim 5 inhibits that normal process, would this be considered "beneficial"...?

- Claim 28 recites a "composition comprising a compound of claim 5, further comprising ...excipients". The implication here is that the composition would be such (i.e., a composition as opposed to a compound) even without the presence of the excipients. Thus, claim 28 appears to be describing a ternary mixture. As such, this claim requires the presence of three different components, yet describes only two of them.

- Claim 35 is drawn to a method of making a composition that comprises a compound of claim 5 and a "potentiating component". The presence of the compound of claim 5 is also recited in step (c) of claim 35. However, claim 35 is omitting an important process step. The claim requires, on the one hand, that the compound of claim 5

winds up being present in the final composition; at the same time, the claim does not require that the compound of claim 5 ever be added. Accordingly, the claim is indefinite as to how the compound of claim 5 appears in the final composition without ever being added.

- Claim 52 is indefinite as to the manifestations of the preservation. This uncertainty arises in part because the method calls for intravenously administering a compound to a donor. Thus, the compound is being administered to a human (or animal); in such a case one would expect "preservation" to occur with or without the compound. Thus, what would be the manifestations of a successful "preservation" that one would not see in the absence of the compound?

✧

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 is rejected under 35 U.S.C. §102(b) as being anticipated by Cherbuliez (*Helv Chimica Acta* **41**, 1163-1168, 1958).

Cherbuliez discloses (table 3, p. 1167) compound 8. This compound is encompassed by claim 5 when the substituent variables correspond as follows:

W = -OH
W = Q (first occurrence)
R = $-CH_2-CH_3$
X = -O-
X = =O

Z = hydrogen
Y = -O-

The response argues that because the possibility of "L" being methylene has been eliminated, and if one assumes that "R" must be methyl, claim 5 cannot encompass the disclosed compound. However, this is found unpersuasive. The fact that "L" can no longer be methylene does not change the analysis at all. This ground of rejection was imposed by defining only the first occurrence of "Q". That is, if the second occurrence of "Q" had never been cited in claim 5, this ground of rejection would have still been imposed, and moreover can be maintained. The response only makes arguments concerning the second of the two occurrences of "Q", and so the rejection is regarded by the examiner as being unrebutted, insofar as the first occurrence of "Q" is concerned.

In addition to the foregoing, the claim is also anticipated for the case of the substituent variables corresponding as follows:

W = -OH
W = Q (second occurrence)
R = $-CH_2-CH_3$
X = O
L = -O-
Z = hydrogen
Y = -O-
m = zero

Thus, for each of two separate reasons, the rejection is maintained.

✧

Claim 5 is rejected under 35 U.S.C. §102(b) as being anticipated by Black (*J. Biol. Chem.* 221, 171-180, 1956).

As indicated previously, Black discloses a compound in each of reactions 1 and 2 which is encompassed by claim 5 when the substituent variables correspond as follows:

W = -OH
R = $-CH_3$
X = =O
X = -S-
Z = OH
Y = -O-

The response points out that claim 5 recites that "X is O or S", and (it is argued) both occurrences of variable "X" must be the same. However, this is found unpersuasive. There is nothing in claim 5 to preclude one of the "X" atoms to be oxygen, and another of the "X" atoms to be sulfur. The fact that the word "indepdently" is not present does not mean that it isn't implied. At best, the claim is ambiguous as to whether the two "X" atoms can be different; however, the skilled chemist familiar with patent disclosures would regard claim 5 as permitting the two X's to be different. But even if claim 5 were amended to explicitly recite that both occurrences of "X" must be identical to one another, this ground of rejection would still be maintained. The reason is that when integer variable "m" is zero, the second of the two formulas (which define "Q") becomes the same as the first of these two formulas, at least in substance. That is, using the second of the two formulas (for "Q"), the claim is anticipated when the variables are as follows:

W = -OH
R = $-CH_3$
X = =O
L = -S-
Z = OH
Y = -O-
m is zero

The rejection is maintained.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton 4/6/04

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